



**University of  
Zurich**<sup>UZH</sup>

**Zurich Open Repository and  
Archive**

University of Zurich  
University Library  
Strickhofstrasse 39  
CH-8057 Zurich  
[www.zora.uzh.ch](http://www.zora.uzh.ch)

---

Year: 2015

---

## **Point of care and factor concentrate-based coagulation algorithms**

Theusinger, Oliver M ; Stein, Philipp ; Levy, Jerrold H

DOI: <https://doi.org/10.1159/000381320>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-123024>

Journal Article

Published Version

Originally published at:

Theusinger, Oliver M; Stein, Philipp; Levy, Jerrold H (2015). Point of care and factor concentrate-based coagulation algorithms. *Transfusion Medicine and Hemotherapy*:115-121.

DOI: <https://doi.org/10.1159/000381320>

# Point of Care and Factor Concentrate-Based Coagulation Algorithms

Oliver M. Theusinger<sup>a</sup> Philipp Stein<sup>a</sup> Jerrold H. Levy<sup>b</sup>

<sup>a</sup>Institute of Anesthesiology, University and University Hospital of Zurich, Zurich, Switzerland;

<sup>b</sup>Cardiothoracic ICU, Duke University School of Medicine, Durham, NC, USA

## Keywords

Bleeding · Cardiac surgery · Goal-directed transfusions · ROTEM® · Thrombelastometry · Transfusion management · Trauma · Point of care devices · POC · Patient blood management

## Summary

In the last years it has become evident that the use of blood products should be reduced whenever possible. There is increasing evidence regarding serious adverse events, including higher mortality and morbidity, related to transfusions. The use of point of care (POC) devices integrated in algorithms is one of the important mechanisms to limit blood product exposure. Any type of algorithm, especially the POC-based ones, allows goal-directed transfusions of blood products and even better targeted factor concentrate substitutions. Different types of algorithms in different surgical settings (cardiac surgery, trauma, liver surgery etc.) have been established with growing interest in their use as they offer objective therapy for management and reduction of blood product use. The use of POC devices with evidence-based algorithms is important in the bleeding patient independent of its origin (traumatic vs. surgical). The use of factor concentrates compared to the classical blood products can be cost-saving, beneficial for the patient, and in agreement with the WHO-requested standard of care. The empiric and uncontrolled use of blood products such as fresh frozen plasma, red blood cells, and platelets without POC monitoring should no longer be followed with regard to actual evidence in literature. Furthermore, the use of factor concentrates may provide better outcomes and potential for cost saving.

## Introduction

Uncontrolled bleeding in trauma or major surgery (e.g. cardiac, liver, orthopedic) leads to a loss of coagulation factors and bears an additional risk for further dilution of coagulation factors by volume replacement. Dilutional coagulopathy impairs coagulation and, if not recognized and promptly and adequately treated by rapid hemostatic interventions, will lead to exsanguination. In 2010 the World Health Organization (WHO) recommended to start using transfusion alternatives and to develop individualized patient blood management programs to reduce transfusion requirements. The patient blood management program consists of three main considerations for management: i) detection and treatment of preoperative anemia, ii) reduction in perioperative RBC loss, and iii) optimizing the patient-specific physiological reserve of anemia (including restrictive hemoglobin transfusion triggers) [1–5].

The purpose of this review is to review the optimal bleeding management by using point of care (POC) devices and transfusion algorithms. This aspect is of major importance as adverse outcome related to blood products (red blood cells (RBCs), fresh frozen plasma (FFP), and platelets) has been proven. The costs can be significantly reduced by lowering blood product administration which may also have the potential to decrease length of hospital stay and to prevent serious adverse events such as infections. Although standard laboratory coagulation tests are widely used to determine coagulopathy in the operating room and for trauma patients in the emergency department, their diagnostic value in the acutely bleeding patient is limited based on turnaround time. Moreover, they have limited predictive value for bleeding and were not developed for the use in actively bleeding patients [6].

The use of POC devices includes whole blood assays such as rotational thromboelastometry or thromboelastography, platelet mapping or platelet aggregometry, and international normalized ratio (INR) / prothrombin time (PT) that will be briefly highlighted in this review [7–9].

**Table 1.** Differences in terms between ROTEM and TEG from Theusinger et al., 2013 [65]

Parameter	ROTEM	TEG
Clot time period to 2 mm amplitude	clotting time (CT)	retraction time (R)
Clot kinetics period from 2 to 20 mm amplitude	clot formation time (CFT)	kinetics (K)
$\alpha$ -angle	slope of tangent at 2 mm amplitude ( $\alpha$ )	slope between R and K ( $\alpha$ )
Maximum clot strength	maximum clot firmness (MCF)	maximum amplitude (MA)
Clot elasticity	maximum clot elasticity (MCE)	G
Lysis at certain points of time	amplitude reduction after 30 or 60 min after MCF (CL30, CL60)	amplitude reduction after 30 or 60 min after MA (Ly30, Ly60)
Clot lysis	maximum lysis (ML)	estimated percent lysis (EPL)

## Point of Care Testing

### PT POC Testing – e.g. CoaguChek®

Besides the CoaguChek® (Roche Diagnostics, Mannheim, Germany), there are various other INR POC devices on the market but because of its use in our institution we stuck to this one. CoaguChek measures the INR and Quick value (In many countries, blood coagulability is expressed in a unit named Quick value. The measured PT is expressed in relation to the coagulation time of a healthy person. The value obtained is the ‘percentage of the standard value’. In a person not receiving oral anticoagulation the ‘normal’ Quick value is between 70 and 100%, but might be different depending on the reagent used according to the calibration against the WHO ‘standard’) in whole blood within 1 min after the addition of 8 µl of blood to the device. These two values are calculated back by the device from a programmed calibrator result. Normally, these results would take 30 to 60 min to be available from the standard laboratory and are obtained by using citrated cell-free plasma. The PT represents the coagulation time in a system that was ‘extrinsically’ activated via factors VII, V and X and the activation of prothrombin to thrombin, which converts fibrinogen to fibrin. This device is ideal to monitor patients taking vitamin K antagonists (e.g. warfarin) in the emergency department, in cardiovascular surgery, in acutely bleeding patients, or in patients with traumatic brain injury; the test can be used for rapid diagnosis and therapy with factor concentrates to rapidly reverse the anticoagulation. The device is also validated to guide outpatient oral anticoagulation (vitamin K antagonists). In the peri-operative setting and the emergency department, however, evidence supporting its use is limited to case series. In 17 patients needing emergency surgery (burr hole, craniotomy, or laminectomy), the anticoagulation was assessed and reversed before the intervention using this assay. The measurements on the CoaguChek correlated well with the laboratory values, and the mean time gained using the POC assay was 47 min [10]. In other settings like war casualties the time gained using this assay was approximately 26 min compared to the laboratory [11]. In ischemic strokes, time to lysis and detection of oral anticoagulants was reduced [12], and in patients after cardiopulmonary bypass PT was determined much earlier than by the laboratory by using this type of POC device [13].

### Clot Formation in Whole Blood Thromboelastography and Rotational Thromboelastometry

The preliminary and most important statement regarding the use of these devices is that, regardless of which results are obtained – even if they are pathological –, a non-bleeding patient needs no therapeutic intervention. All standard coagulation tests in the laboratory are measured in plasma and assess usually extrinsic and an intrinsic pathways using PT and partial thromboplastin time, respectively. Only the clotting time is measured, giving no information about the following development or stability of the blood clot.

In 1948 Hartert [14] first presented a method to measure the formation of a clot from whole blood. Almost 50 years passed until thromboelastography (TEG® by Hemoscope Corporation, Niles, IL, USA) and rotational thromboelastometry (ROTEM®; initially by Pentapharm, now TEM International GmbH, Munich, Germany) were developed and made registered trademarks in 1996 and 2000, respectively. Today, these two systems are the most commonly used POC devices for whole blood coagulation diagnostic testing in trauma, liver surgery, cardiac surgery, post-partum hemorrhage, and many other settings. They provide valuable information about clot initiation, formation, and lysis corresponding to platelet number and function, fibrinogen quantity and function as well as pro- and anticoagulation enzymes. Measurements are usually made using citrated whole blood. Reagents and whole blood are pipetted and incubated in heated (37 °C) small cups. A pin is introduced into the sample measuring the changes of the viscoelastic properties of the forming blood clot. In TEG, the cup oscillates with an angle of 4.45°, and the consecutive movement of the pin is translated into an electric signal by a torsion wire. In ROTEM, the cup is stationary and the pin moves 4.75°; the impedance of pin rotation is measured by an optical detector [15]. Information is gained by the initiation of clot formation, clot formation itself, maximum clot firmness, and clot lysis. Terminology in TEG and ROTEM is different and summarized in table 1.

The ROTEM device can measure 4 channels in parallel. Five commonly used different tests can be started, and the clot formation can be visualized. With EXTEM, coagulation is started by the addition of tissue factor, representing the classical extrinsic pathway activation. With INTEM, coagulation is initiated by contact

activator leading to intrinsic pathway activation. The inhibition of the platelets by cytochalasin D in the FIBTEM test shows the fibrinogen clotting which corresponds to fibrinogen plasma levels and can be visualized [16, 17]. Furthermore the amount of factor XIII plays a role regarding the maximal amplitude of this test [18]. No effect of platelets should be present anymore as they were completely inhibited by cytochalasin D.

The addition of aprotinin, which is called APTEM test, inhibits fibrinolysis, and addition of heparinase before contact activation visualizes a heparin effect in the HEPTEM test.

In most active bleeding patient the first substrate to drop below critical levels will be fibrinogen. ROTEM is capable to determine indirectly fibrinogen concentration (as 7 mm correspond to 1.5 g/l, a curve regarding this correlation exists in the literature) within 10 min, which normally takes 30–60 min in the laboratory, and the efficacy of treatment can be readily determined [7, 19–22]. Hyperfibrinolysis can be readily detected by TEG and ROTEM. Reduction of clot strength or complete lysis after formation is the in vitro equivalent of pathological activation of fibrinolysis. Trauma patients with hyperfibrinolysis documented by ROTEM have a significantly higher mortality compared to those without [23]. Hyperfibrinolysis > 3% is associated with massive transfusion [24]. Fibrinogen substitution as a substrate and prothrombin complex concentrate as an enzyme, guided by rotational thrombelastometry, can be safely used to enhance thrombin generation in patients with severe multiple trauma [25–27]. Moreover the FIBTEM value can be used to predict massive transfusion in trauma [28]. ROTEM-guided coagulation management was associated with reduced transfusion rates of allogeneic blood products [21]. In pediatric cardiac surgery, thrombelastometry-guided coagulation management reduced bleeding and the use of allogeneic RBC transfusion and length of stay on the intensive care unit [29]. However, these tests are not readily suited for monitoring the oral anticoagulant agents. Also, vitamin K antagonists are not readily measured unless severely over-anticoagulated. Novel or directly acting oral anticoagulants alter viscoelastic tests. Their exact effect is difficult to quantify, although work is underway to develop specific tests [30].

#### *Qualification and Quantification of Platelet Function or Inhibition*

Different POC devices dealing with platelet function exist. The PFA-100® (Siemens Healthcare, Malvern, PA, USA) measures platelet adhesion, mimicking arterial high shear stress. Addition of whole blood measures a ‘closure time’ in collagen/epinephrine and collagen/ADP test cartridges. Information about inborn platelet function defects and von Willebrand disease can be obtained from this test [31]. However, its use in a bleeding and coagulopathic patient is not well characterized as many of these tests may not work with dilutional coagulopathy.

Multiplate® and TEG platelet mapping™ are POC devices to detect and quantify the effect of antiplatelet medication. Inhibition of the arachidonic acid pathway, the GPIIb/IIIa pathway, and the ADP (P2Y12) receptor pathway can be measured.

Multiplate® (Roche Diagnostics International Ltd, Rotkreuz, Switzerland) visualizes electrode coating by aggregated platelets leading to aggregation units (over time). Low volumes of whole blood in five channels (dual sensors) measure platelet inhibition by stimulation with arachidonic acid (ASPItest), adenosine diphosphate (ADPtest), collagen (COLtest), and thrombin receptor-activating peptide (TRAPtest).

The number of patients treated with antiplatelet drugs due to cardiovascular or cerebrovascular disease is continuously increasing [32]. New ADP receptor antagonists with specific pharmacokinetic and pharmacodynamic profiles like Ticagrelor® make a quantification of the clinical antiplatelet effect critical. Even for high-risk patients with drug-eluting stents needing emergency surgery, POC testing may be desired to guide a bridging protocol when one or two of the antiplatelet drugs are to be discontinued. Moreover, patients not responding to clopidogrel treatment can be identified [33]. Some institutions treat these patients without using these devices – the standard of care has to be determined yet.

After on-pump aorto-coronary bypass (CABG) surgery, TEG platelet mapping was able to predict excessive postoperative chest tube bleeding (CTB) and the need for platelet transfusion [34], but failed to correlate with 24-hour CTB [35]. Other platelet function testing failed to predict postoperative bleeding in patients with P2Y12 inhibitors [36, 37]. PFA-100 had a high negative predictive value of 98% to identify patients not needing platelet transfusions post cardiac bypass [38]. VerifyNow® (Accumetrics, San Diego, CA, USA) platelet function assay predicted the need for RBC transfusion, but not the need for platelet transfusion post CABG [39]. Platelet dysfunction measured by POC (collagen-activated platelet count) during rewarming was associated with high (>1,770 ml) blood loss in a cohort of 100 patients [40].

In neurosurgery, antiplatelet drugs were a risk factor for re-bleeding after neurosurgical procedures [41]. Patients with impaired platelet function due to aspirin intake had higher mortality in the case of spontaneous intracranial hemorrhage [42]. Inability to normalize the VerifyNow aspirin assay value was associated with a trend towards higher mortality [43]. Of note, the use of platelet transfusions to normalize platelet function in patients with intracranial hemorrhage did not show a positive effect on patient outcome in retrospective analyses [44, 45].

In severe brain trauma, platelet dysfunction was present due to a significantly increased inhibition of platelet ADP and arachidonic acid receptors [46]. In 46 trauma patients reported to be taking clopidogrel, the platelet inhibitory effect was measured with VerifyNow (P2Y12). Patients with low (<30%) platelet inhibition by clopidogrel did not die due to bleeding and had low rates of increased intracranial hemorrhage [47]. Using the multiple electrode aggregometry in 163 trauma patients, a retrospective analysis identified significant difference in the ADPtest between survivors and non-survivors [48]. The latest device, named TEM Platelet®, was developed by TEM International GmbH (Munich, Germany); this two-channel device measures platelet function by aggregometry and can be added to the ROTEM, allowing to meas-



**Table 2.** Cost / blood product savings by the first published algorithms using POC devices

Publication	Type	Year	Field	Patients	Mortality	Savings of cost
O'Keefe et al. [66]	retrospective	2008	trauma	132	52.3%	22%
Despotis et al. [67]	prospective	1994	cardiac	66	n.n.	reduction
Spiess et al. [68]	retrospective	1995	cardiac	1,079	n.n.	USD 50,000.00 in 6 months
Shore-Lesserson et al. [69]	prospective	1999	cardiac	92	n.n.	blood products –20%
Nuttall et al. [70]	prospective	2001	cardiac	58	n.n.	FFP and platelets –60%
Capraro et al. [71]	prospective	2001	cardiac	58	3%	blood products –20%
Royston et al. [72]	prospective	2001	cardiac	120	n.n.	FFP and platelets –70%
Avidan et al. [73]	prospective	2004	cardiac	220	n.n.	RBCs, platelets –60%; FFP –90%

ure in total 6 channels with complete coagulation assessment and platelet function. POC monitoring of blood coagulation at the bedside is not only desirable but also is becoming increasingly recommended [7].

### Factor Concentrates

The use of FFP leads to adverse effects, including increased mortality, multiple organ failure, risk of infection, lung injury, and immunomodulation [49, 50]. The effectiveness of FFP compared to fibrinogen concentrate regarding clinical endpoints as blood loss, transfusion requirements, hospital length of stay, survival and plasma fibrinogen concentration favors fibrinogen concentrates [49]. For this reason fibrinogen and potentially other factor concentrates should be considered in patients with substantial bleeding [7].

This consideration is based on target levels of fibrinogen for trauma patients that have been defined at 1.5–2.0 g/l in the European Trauma Treatment Guidelines [7]. Administration of fibrinogen concentrates is advantageous compared to FFP transfusion as fibrinogen concentration in FFP is variable (about 2 g/l on average), and large volumes of FFP would be necessary to effectively increase the fibrinogen concentration to achieve target fibrinogen concentrations of 1.5–2.0 g/l [51]. When replacing most FFP transfusions with fibrinogen concentrate, monitoring factor XIII levels is also advisable after the replacement of approximately 50% of the blood volume as this will be the moment when factor XIII reaches a critical level. A 60% factor XIII activity level is advised to be maintained by the administration of factor XIII concentrate [19, 52–54].

Besides single-factor concentrates, prothrombin complex concentrates (PCCs) are also part of factor-based algorithms [19, 21, 22, 32, 56, 55]. Individual PCCs differ regarding their factors contained, their relative composition, and their thrombotic potential. Although PCCs are approved for vitamin K antagonist reversal [57], their use is also suggested by the update of the European Trauma Guidelines in 2013 if the initiation of clot formation is prolonged in rotational thromboelastometry [7]. PCC should be used only within a strict algorithm, the dose should be small, and repeat doses should be given with caution to minimize thrombotic

risks [56]. Of note, studies indicate that significant reductions in RBCs, FFP and platelets transfusions can be facilitated by using a coagulation factor concentrate-based coagulopathy management in trauma patients [58]. Based upon data from four European countries (UK, Germany, Italy, and Switzerland), blood substitution levels and blood products were calculated and found to account for approximately 27% of all costs associated with trauma care on the intensive care unit [59]. Additional findings include a reduction in septic complications and organ failure which translated into trends towards reduced ventilator time and shorter overall in-hospital length of stays. These important findings may also contribute to cost reduction in acute trauma care without increasing the risk for the individual patient.

### Algorithms Used

The first types of algorithm published used TEG/ROTEM to guide the administration of blood products such as platelets and FFP. They were all able to reduce blood product use and costs. Most studies were first performed in cardiac surgery in 1994. In table 2 a brief overview of the first publications is given regarding cost-savings.

However, depending on the country, different factor concentrates may not be available. The following examples show sophisticated algorithms which give clear instructions regarding the treatment of a bleeding patient depending on the results given by POC devices. Görlinger et al. [32] published in 2011 their 5-year experience in cardiac surgery in Essen, Germany. They used an algorithm in which ROTEM and Multiplate was integrated and which gave clearly structured therapeutical instructions. Thus they were able to significantly reduce the use of any allogeneic blood transfusion (52.5 vs. 42.2%;  $p < 0.0001$ ), of packed RBCs (49.7 vs. 40.4%;  $p < 0.0001$ ), and of FFP (19.4 vs. 1.1%;  $p < 0.0001$ ). The amount of platelets transfused (10.1 vs. 13.0%;  $p = 0.0041$ ) as well as the administration of fibrinogen concentrate (3.73 vs. 10.01%;  $p < 0.0001$ ) and PCC (4.42 vs. 8.9%;  $p < 0.0001$ ) increased significantly. During the course of the study, a switch from aprotinin to tranexamic acid occurred as well as an increase in the use of dual antiplatelet therapy (2.7 vs. 13.7%;  $p < 0.0001$ ); as a consequence the incidence of massive ( $\geq 10$  U packed RBCs) transfu-

sion (2.5 vs. 1.26%;  $p = 0.0057$ ) and unplanned re-exploration (4.19 vs. 2.24%;  $p = 0.0007$ ) decreased. Thrombotic and thromboembolic events also decreased significantly (3.19 vs. 1.77%;  $p = 0.0115$ ), but in-hospital mortality remained identical.

In another study by Schöchl et al. [21], a ROTEM-guided algorithm was used in trauma patients to compare patients receiving FFP versus those receiving fibrinogen concentrates and PPC instead. As hemostatic therapy in the emergency department and during surgery the FFP group (injury severity score  $35.5 \pm 10.5$ ) received a median of 6 (range 2–51) units of FFP, while the fibrinogen-PCC group (injury severity score  $35.2 \pm 12.5$ ) received a median of 6 (range 0–15) g of fibrinogen concentrate and 1,200 (range 0–6,600) U of PCC. RBC transfusion was avoided in 29% of patients in the fibrinogen-PCC group, compared with only 3% in the FFP group ( $p < 0.001$ ). Transfusion of platelet concentrate was avoided in 91% of patients in the fibrinogen-PCC group, compared with 56% in the FFP group ( $p < 0.001$ ). Mortality was comparable in both groups – 7.5% in the fibrinogen-PCC group and 10.0% in the FFP group ( $p = 0.69$ ). This study also showed a clear benefit for using an algorithm guided by POC devices.

The third example to be mentioned is the algorithm published by Theusinger et al. [60, 61]. This algorithm also takes into consideration different laboratory and POC results, such as ROTEM, CoaguCheck and Multiplate, and gives clear treatment orders. Depending on the type of surgery – neurosurgery and cardiac surgery – versus trauma and others, the threshold values have been adapted to take into consideration different bleeding risks. A FIBTEM with a maximum clot firmness (MCF) of  $<7$  mm, corresponding to approximately 1.5 g/dl of fibrinogen, only needs substitution of fibrinogen if the patient is bleeding; in a non-bleeding patient no therapeutic intervention is needed. Platelets need to be above 100,000/ $\mu$ l in the bleeding patient during neurosurgery and cardiac surgery compared to 50,000/ $\mu$ l in all others. This algorithm aims to correct pathological values only in case of bleeding and to reach normal values at the lower range to avoid thromboembolic compli-

cations. This algorithm also includes desmopressin which enhances platelet adherence and is the first choice in the treatment of bleeding patients with quantitative deficiency (type 1) and some of the qualitative defects (type 2) of von Willebrand factor (vWF) [62, 63]. Patients treated with aspirin and ADP receptor inhibitors such as clopidogrel could also benefit from POC testing to assess the individual efficacy of desmopressin treatment [64]. In case of insufficient treatment with desmopressin, transfusing platelets is the ultimate option.

## Conclusion

The use of POC devices with evidence-based algorithms seems mandatory in the bleeding patient independent of bleeding origin (traumatic vs. surgical). The use of factor concentrates, compared to the classical blood products, is cost-saving and beneficial for the patient and also in agreement with the WHO-requested standard of care. The uncontrolled use of blood products such as FFP, RBCs and platelets without POC control seems to be inadequate with regard to the actual evidence in literature. Furthermore, the use of factor concentrates seems to be in favor for better outcome and cost saving.

## Disclosure Statement

Oliver M. Theusinger has received honoraria or travel support for consulting or lecturing from the following companies: CSL Behring Schweiz, Zurich, Switzerland; Vifor SA, Villars-sur-Glâne, Switzerland; Roche Pharma (Schweiz) AG, Reinach, Switzerland; Pentapharm AG, Munich, Germany; TEM International, Munich, Germany.

Philipp Stein has no conflict of interest.

Within the past 3 years Jerrold H. Levy has served or serves on research steering committees, data safety monitoring boards, or advisory boards for CSL Behring, Boehringer-Ingelheim, Grifols, J&J, Marathon, Merck, Medicines Company, Octapharma, Portola, and Roche.

## References

- Carson JL, Carless PA, Hebert PC: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. *Cochrane Database Syst Rev* 2012;4:CD0002042.
- Goodnough LT, Shander A: Patient blood management. *Anesthesiology* 2012;116:1367–1376.
- Shander A, Hofmann A, Isbister J, Van Aken H: Patient blood management – the new frontier. *Best Pract Res Clin Anaesthesiol* 2013;27:5–10.
- Spahn DR, Goodnough LT: Alternatives to blood transfusion. *Lancet* 2013;381:1855–1865.
- Williamson LM, Devine DV: Challenges in the management of the blood supply. *Lancet* 2013;381:1866–1875.
- Park MS, Martini WZ, Dubick MA, Salinas J, Butenas S, Kheirabadi BS, Pusateri AE, Vos JA, Guymon CH, Wolf SE, Mann KG, Holcomb JB: Thromboelastography as a better indicator of hypercoagulable state after injury than prothrombin time or activated partial thromboplastin time. *J Trauma* 2009;67:266–276.
- Spahn DR, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernandez-Mondejar E, Filipescu D, Hunt BJ, Komadina R, Nardi G, Neugebauer E, Ozier Y, Riddez L, Schultz A, Vincent JL, Rossaint R: Management of bleeding and coagulopathy following major trauma: an updated European guideline. *Crit Care* 2013;17:R76.
- Davenport R, Manson J, De'Ath H, Platten S, Coates A, Allard S, Hart D, Pearce R, Pasi KJ, MacCallum P, Stanworth S, Brohi K: Functional definition and characterization of acute traumatic coagulopathy. *Crit Care Med* 2011;39:2652–2658.
- Johansson PI, Stissing T, Bochen L, Ostrowski SR: Thrombelastography and tromboelastometry in assessing coagulopathy in trauma. *Scand J Trauma Resusc Emerg Med* 2009;17:45.
- Beynon C, Jakobs M, Rizos T, Unterberg AW, Sakowitz OW: Rapid bedside coagulometry prior to urgent neurosurgical procedures in anticoagulated patients. *Br J Neurosurg* 2014;28:29–33.
- Cotte J, D'Aanda E, Chauvin V, Kaiser E, Meaudre E: Point-of-care coagulation testing for trauma patients in a military setting: a prospective study. *J Spec Oper Med* 2013;13:59–62.
- Nusa D, Harvey I, Almansouri AY, Wright S, Neeman T, Ahmad O, Hughes AR, Lueck CJ: Assessment of point-of-care measurement of international normalized ratio using the CoaguChek XS plus system in the setting of acute ischaemic stroke. *Intern Med J* 2013;43:1205–1209.
- Chavez JJ, Weatherall JS, Strevels SM, Liu F, Snider CC, Carroll RC: Evaluation of a point-of-care coagulation analyzer on patients undergoing cardiopulmonary bypass surgery. *J Clin Anesth* 2004;16:7–10.
- Hartert H: Blutgerinnungsstudien mit der Thrombelastographie, einem neuen Untersuchungsverfahren. *Klin Wochenschr* 1948;26:577–583.
- Luddington RJ: Thrombelastography/thromboelastometry. *Clin Lab Haematol* 2005;27:81–90.

- 16 Theusinger OM, Nurnberg J, Asmis LM, Seifert B, Spahn DR: Rotation thromboelastometry (ROTEM) stability and reproducibility over time. *Eur J Cardiothorac Surg* 2010;37:677–683.
- 17 Hiippala ST: Dextran and hydroxyethyl starch interfere with fibrinogen assays. *Blood Coagul Fibrinolysis* 1995;6:743–746.
- 18 Theusinger OM, Baulig W, Asmis LM, Seifert B, Spahn DR: In vitro factor XIII supplementation increases clot firmness in rotation thromboelastometry (ROTEM). *Thromb Haemost* 2010;104:385–391.
- 19 Theusinger OM, Madjdpour C, Spahn DR: Resuscitation and transfusion management in trauma patients: emerging concepts. *Curr Opin Crit Care* 2012;18:661–670.
- 20 Rossaint R, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernandez-Mondejar E, Hunt BJ, Komadina R, Nardi G, Neugebauer E, Ozier Y, Riddez L, Schultz A, Stahel PF, Vincent JL, Spahn DR; Task Force for Advanced Bleeding Care in Trauma: Management of bleeding following major trauma: an updated European guideline. *Crit Care* 2010;14:R52.
- 21 Schochl H, Nienaber U, Maegele M, Hochleitner G, Primavesi F, Steitz B, Arndt C, Hanke A, Voelckel W, Solomon C: Transfusion in trauma: thromboelastometry-guided coagulation factor concentrate-based therapy versus standard fresh frozen plasma-based therapy. *Crit Care* 2011;15:R83.
- 22 Theusinger OM, Felix C, Spahn DR: Strategies to reduce the use of blood products: a European perspective. *Curr Opin Anaesthesiol* 2012;25:59–65.
- 23 Theusinger OM, Wanner GA, Emmert MY, Billeter A, Eismen J, Seifert B, Simmen HP, Spahn DR, Baulig W: Hyperfibrinolysis diagnosed by rotational thromboelastometry (ROTEM) is associated with higher mortality in patients with severe trauma. *Anesth Analg* 2011;113:1003–1012.
- 24 Chapman MP, Moore EE, Ramos CR, Ghasabian A, Harr JN, Chin TL, Stringham JR, Sauaia A, Silliman CC, Banerjee A: Fibrinolysis greater than 3% is the critical value for initiation of antifibrinolytic therapy. *J Trauma Acute Care Surg* 2013;75:961–967.
- 25 Schlump CJ, Voelckel W, Inaba K, Maegele M, Schochl H: Impact of fibrinogen concentrate alone or with prothrombin complex concentrate (+/- fresh frozen plasma) on plasma fibrinogen level and fibrin-based clot strength (FIBTEM) in major trauma: a retrospective study. *Scand J Trauma Resusc Emerg Med* 2013;21:74.
- 26 Schochl H, Schlump CJ, Voelckel W: Perioperative coagulation management in multiple trauma patients based on viscoelastic test results (in German). *Unfallchirurg* 2014;117:111–117.
- 27 Schochl H, Forster L, Woidke R, Solomon C, Voelckel W: Use of rotation thromboelastometry (ROTEM) to achieve successful treatment of polytrauma with fibrinogen concentrate and prothrombin complex concentrate. *Anaesthesia* 2010;65:199–203.
- 28 Schochl H, Cotton B, Inaba K, Nienaber U, Fischer H, Voelckel W, Solomon C: FIBTEM provides early prediction of massive transfusion in trauma. *Crit Care* 2011;15:R265.
- 29 Nakayama Y, Nakajima Y, Tanaka KA, Sessler DI, Maeda S, Iida J, Ogawa S, Mizobe T: Thromboelastometry-guided intraoperative haemostatic management reduces bleeding and red cell transfusion after paediatric cardiac surgery. *Br J Anaesth* 2015;114:91–102.
- 30 Casutt M, Konrad C, Schuepfer G: Effect of rivaroxaban on blood coagulation using the viscoelastic coagulation test ROTEM™. *Anaesthesist* 2012;61:948–953.
- 31 Franchini M: The platelet function analyzer (PFA-100): an update on its clinical use. *Clin Lab* 2005;51:367–372.
- 32 Görlinger K, Dirkmann D, Hanke AA, Kamler M, Kotenberg E, Thielmann M, Jakob H, Peters J: First-line therapy with coagulation factor concentrates combined with point-of-care coagulation testing is associated with decreased allogeneic blood transfusion in cardiovascular surgery: a retrospective, single-center cohort study. *Anesthesiology* 2011;115:1179–1191.
- 33 Hazarbasanov D, Velchev V, Finkov B, Postadjian A, Kostov E, Rifai N, Aradi D: Tailoring clopidogrel dose according to multiple electrode aggregometry decreases the rate of ischemic complications after percutaneous coronary intervention. *J Thromb Thrombolysis* 2012;34:85–90.
- 34 Chowdhury M, Shore-Lesserson L, Mais AM, Leyvi G: Thromboelastograph with platelet mapping™ predicts postoperative chest tube drainage in patients undergoing coronary artery bypass grafting. *J Cardiothorac Vasc Anesth* 2014;28:217–223.
- 35 Carroll RC, Chavez JJ, Snider CC, Meyer DS, Muenchen RA: Correlation of perioperative platelet function and coagulation tests with bleeding after cardiopulmonary bypass surgery. *J Lab Clin Med* 2006;147:197–204.
- 36 Yu PJ, Cassiere HA, Dellis SL, Manetta F, Stein J, Hartman AR: P2y12 platelet function assay for assessment of bleeding risk in coronary artery bypass grafting. *J Cardiac Surg* 2014;29:312–316.
- 37 Dietrich GV, Schueck R, Menges T, Kiesenbauer NP, Fruehauf AC, Marquardt I: Comparison of four methods for the determination of platelet function in whole blood in cardiac surgery. *Thromb Res* 1998;89:295–301.
- 38 Slaughter TF, Sreeram G, Sharma AD, El-Moalem H, East CJ, Greenberg CS: Reversible shear-mediated platelet dysfunction during cardiac surgery as assessed by the PFA-100 platelet function analyzer. *Blood Coagul Fibrinolysis* 2001;12:85–93.
- 39 Alstrom U, Granath F, Oldgren J, Stahle E, Tyden H, Siegbahn A: Platelet inhibition assessed with Verifynow, flow cytometry and Platelet Mapping in patients undergoing heart surgery. *Thromb Res* 2009;124:572–577.
- 40 Orlov D, McCluskey SA, Selby R, Yip P, Pendergrast J, Karkouti K: Platelet dysfunction as measured by a point-of-care monitor is an independent predictor of high blood loss in cardiac surgery. *Anesth Analg* 2014;118:257–263.
- 41 Palmer JD, Sparrow OC, Iannotti F: Postoperative hematoma: a 5-year survey and identification of avoidable risk factors. *Neurosurgery* 1994;35:1061–1065.
- 42 Naidech AM, Bernstein RA, Levasseur K, Bassin SL, Bendok BR, Batjer HH, Bleck TP, Alberts MJ: Platelet activity and outcome after intracerebral hemorrhage. *Ann Neurol* 2009;65:352–356.
- 43 Bachelani AM, Bautz JT, Sperry JL, Corcos A, Zenati M, Billiar TR, Peitzman AB, Marshall GT: Assessment of platelet transfusion for reversal of aspirin after traumatic brain injury. *Surgery* 2011;150:836–843.
- 44 Campbell PG, Sen A, Yadla S, Jabbar P, Jallo J: Emergency reversal of antiplatelet agents in patients presenting with an intracranial hemorrhage: a clinical review. *World Neurosurg* 2010;74:279–285.
- 45 Nishijima DK, Zehtabchi S, Berrong J, Legome E: Utility of platelet transfusion in adult patients with traumatic intracranial hemorrhage and preinjury antiplatelet use: a systematic review. *J Trauma Acute Care Surg* 2012;72:1658–1663.
- 46 Davis PK, Musunuru H, Walsh M, Cassidy R, Yount R, Losiniecki A, Moore EE, Wohlauer MV, Howard J, Ploplis VA, Castellino FJ, Thomas SG: Platelet dysfunction is an early marker for traumatic brain injury-induced coagulopathy. *Neurocrit Care* 2013;18:201–208.
- 47 Bansal V, Fortlage D, Lee J, Doucet J, Potenza B, Coimbra R: A new clopidogrel (Plavix) point-of-care assay: rapid determination of antiplatelet activity in trauma patients. *J Trauma* 2011;70:65–70.
- 48 Solomon C, Traintinger S, Ziegler B, Hanke A, Rahe-Meyer N, Voelckel W, Schochl H: Platelet function following trauma. A multiple electrode aggregometry study. *Thromb Haemost* 2011;106:322–330.
- 49 Mahambrey T, Pendry K, Nee A, Bonney S, Nee PA: Critical care in emergency department: massive haemorrhage in trauma. *Emerg Med J* 2013;30:9–14.
- 50 Spahn DR, Rossaint R: Coagulopathy and blood component transfusion in trauma. *Br J Anaesth* 2005;95:130–139.
- 51 Theusinger OM, Baulig W, Seifert B, Emmert MY, Spahn DR, Asmis LM: Relative concentrations of haemostatic factors and cytokines in solvent/detergent-treated and fresh-frozen plasma. *Br J Anaesth* 2011;106:505–511.
- 52 Theusinger OM, Spahn DR, Ganter MT: Transfusion in trauma: why and how should we change our current practice? *Curr Opin Anaesthesiol* 2009;22:305–312.
- 53 Godje O, Gallmeier U, Schelian M, Grunewald M, Mair H: Coagulation factor XIII reduces postoperative bleeding after coronary surgery with extracorporeal circulation. *Thorac Cardiovasc Surg* 2006;54:26–33.
- 54 Theusinger OM: The inhibiting effect of factor XIII on hyperfibrinolysis. *Anesth Analg* 2012;114:1149–1150.
- 55 Schochl H, Nienaber U, Hofer G, Voelckel W, Jambor C, Scharbert G, Kozek-Langenecker S, Solomon C: Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM)-guided administration of fibrinogen concentrate and prothrombin complex concentrate. *Crit Care* 2010;14:R55.
- 56 Sorensen B, Spahn DR, Innerhofer P, Spannagl M, Rossaint R: Clinical review: prothrombin complex concentrates – evaluation of safety and thrombogenicity. *Crit Care* 2011;15:201.
- 57 Preston FE, Laidlaw ST, Sampson B, Kitchen S: Rapid reversal of oral anticoagulation with warfarin by a prothrombin complex concentrate (Beriplex): Efficacy and safety in 42 patients. *Br J Haematol* 2002;116:619–624.
- 58 Nienaber U, Innerhofer P, Westermann I, Schochl H, Attal R, Breitkopf R, Maegele M: The impact of fresh frozen plasma vs coagulation factor concentrates on morbidity and mortality in trauma-associated haemorrhage and massive transfusion. *Injury* 2011;42:697–701.
- 59 Pape HC, Neugebauer E, Ridley Saxon A, Chiara O, Nielsen TG, Christensen CM: Cost-drivers in acute treatment of severe trauma in Europe: a systematic review of literature. *Eur J Trauma Emerg Surg* 2009;35:61–66.
- 60 Theusinger OM, Stein P, Spahn DR: Transfusion strategy in multiple trauma patients. *Curr Opin Crit Care* 2014;20:646–655.
- 61 Theusinger OM, Stein P, Spahn DR: Applying ‘patient blood management’ in the trauma center. *Curr Opin Anaesthesiol* 2014;27:225–232.
- 62 Ruggeri ZM, Mannucci PM, Lombardi R, Federici AB, Zimmerman TS: Multimeric composition of factor VIII/von Willebrand factor following administration of DDAVP: implications for pathophysiology and therapy of von Willebrand’s disease subtypes. *Blood* 1982;59:1272–1278.
- 63 Castaman G, Goodeve A, Eikenboom J, European Group on von Willebrand Disease: Principles of care for the diagnosis and treatment of von Willebrand disease. *Haematologica* 2013;98:667–674.
- 64 Beynon C, Sakowitz OW, Unterberg AW: Multiple electrode aggregometry in antiplatelet-related intracerebral haemorrhage. *J Clin Neurosci* 2013;20:1805–1806.

- 65 Theusinger OM, Levy JH: Point of care devices for assessing bleeding and coagulation in the trauma patient. *Anesthesiol Clin* 2013;31:55–65.
- 66 O’Keeffe T, Refaai M, Tchorz K, Forestner JE, Sarode R: A massive transfusion protocol to decrease blood component use and costs. *Arch Surg* 2008;143:686–690; discussion 690–691.
- 67 Despotis GJ, Grishaber JE, Goodnough LT: The effect of an intraoperative treatment algorithm on physicians’ transfusion practice in cardiac surgery. *Transfusion* 1994;34:290–296.
- 68 Spiess BD, Gillies BS, Chandler W, Verrier E: Changes in transfusion therapy and reexploration rate after institution of a blood management program in cardiac surgical patients. *J Cardiothorac Vasc Anesth* 1995;9:168–173.
- 69 Shore-Lesserson L, Manspeizer HE, DePerio M, Francis S, Vela-Cantos F, Ergin MA: Thromboelastography-guided transfusion algorithm reduces transfusions in complex cardiac surgery. *Anesth Analg* 1999;88:312–319.
- 70 Nuttall GA, Oliver WC, Santrach PJ, Bryant S, Dearani JA, Schaff HV, Ereth MH: Efficacy of a simple intraoperative transfusion algorithm for nonerythrocyte component utilization after cardiopulmonary bypass. *Anesthesiology* 2001;94:773–781; discussion 5A–6A.
- 71 Capraro L, Kuitunen A, Salmenpera M, Kekomaki R: On-site coagulation monitoring does not affect hemostatic outcome after cardiac surgery. *Acta Anaesthesiol Scand* 2001;45:200–206.
- 72 Royston D, von Kier S: Reduced haemostatic factor transfusion using heparinase-modified thrombelastography during cardiopulmonary bypass. *Br J Anaesth* 2001;86:575–578.
- 73 Avidan MS, Alcock EL, Da Fonseca J, Ponte J, Desai JB, Despotis GJ, Hunt BJ: Comparison of structured use of routine laboratory tests or near-patient assessment with clinical judgement in the management of bleeding after cardiac surgery. *Br J Anaesth* 2004;92:178–186.